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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,435	08/01/2001	Yuriy M. Dunayevskiy	HKI-106AX	6450

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EXAMINER

EPPERSON, JON D

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 09/02/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary***P/E Copy***Application No.**

09/920,435

**Applicant(s)**

DUNAYEVSKIY ET AL.

**Examiner**

Jon D Epperson

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14, 21 and 22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14, 21 and 22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Status of the Application***

1. The Response filed June 27, 2003 (Paper No. 9) is acknowledged.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Status of the Claims***

3. Claims 1-14 and 21-22 were pending in the present Application (claims 15-20 were withdrawn by the Examiner in Paper No. 7). Applicants amended claims 3 and 13 in Paper No. 9. Therefore, claims 1-14 and 21-22 are still pending and examined on the merits.
4. This application contains claims 15-20 drawn to a nonelected invention(s) (see Paper No. 7). This was addressed in the previous action. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

### **Withdrawn Objections/Rejections**

5. With respect to the rejections under the second paragraph of 35 U.S.C. 112, the rejections denoted B-C are withdrawn in view of applicant's amendments to the claims and/or cancellation of claims. All other rejections are maintained and the arguments are addressed below.

**Outstanding Objections and/or Rejections**

***Claims Rejections - 35 U.S.C. 112, second paragraph***

6. Claims 1-14 and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claims 1 and 14**, the term “natural” is indefinite and/or unclear. The term is vague and indefinite because it is not clear how one of ordinary skill in the art would be able to identify a “natural” sample from an “unnatural” sample. Absent of a teaching of all naturally occurring samples, one would not be able to determine which were or were not made by a natural process because both the “natural” and “unnatural” samples would have the same structures i.e., you couldn’t tell just by looking at them. Consequently, it is not possible to determine the metes and bounds of the invention as claimed despite the examples provided applicants (e.g., see specification, page 8, last paragraph). A claim to a material defined solely in terms of its origins i.e., the way it was made e.g., a natural process does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a sample made in nature i.e., a “natural” sample.

Furthermore, what if a person of skill in the art were to “synthesize” all the components of a “natural” sample. Would the sample still be considered “natural”?

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Would the scope of Applicants claims change as more “natural” samples are synthesized commercially?

Therefore, claims 1 and 14 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. Withdrawn.

C. Withdrawn.

D. Withdrawn.

*Response*

7. Applicant’s arguments directed to the above 35 U.S.C. 112, second paragraph rejections were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants’ newly amended and/or added claims and/or newly amended arguments.

A. Applicants argue that the term “natural” is clear in light of the specification. Specifically, applicants contend that on page 2 of the specification, first full paragraph, natural samples encompass those that are highly and chemically diverse collection of compounds that include very small to very large molecules, which makes it difficult to isolate any single active compound. Applicants further state that examples of “natural” compounds have been provided in the specification like the ones listed on page 8 of the specification, last full paragraph. Applicants further state that one of ordinary skill in the

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art of the invention would understand that “natural” sample refers to a “naturally” occurring biological material, such as plant matter, animal matter, extracts from such materials and he like. In contrast, samples other than natural samples distinguished in the specification are combinatorial libraries, which are made synthetically containing a large number of different chemicals.

This is not found persuasive for the following reasons:

As an initial matter the Examiner notes that Applicants have not addressed the points made in the original rejection. Specifically, the Examiner stated, “one would not be able to determine which were or were not made by a natural process because both the ‘natural’ and ‘unnatural’ samples would have the same structures i.e., you couldn’t tell just by looking at them.” Here, the Examiner maintains that the “natural” process for making a sample (i.e., a natural sample) does not impart any discernable “structural features” to the compounds within the sample that could distinguish it from an “unnatural” sample and, as a result, it is not clear how the term “natural” further limits the term sample. What distinguishing structural features do “natural” samples have that “unnatural” samples do not? It would appear to the examiner that both “natural” and “unnatural” samples could be composed of compounds that are both “large” and “small” and “difficult” to isolate.

Furthermore, Applicants cited passages (see above) do not cure this defect because Applicants’ specification provides only an ambiguous definition for the term. For example, Applicants cite the first full paragraph on page 2 (see Paper No. 9, page 6, last paragraph) wherein natural samples are defined as “highly and chemically diverse

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collection of compounds that include very small to very large molecules, which makes it very difficult to isolate an single active compound” (see specification, page 2, paragraph 1). The Examiner contends that this definition is inadequate. For example, Applicants use relative terms like “highly and chemically diverse” and “very small to very large” and “difficult to isolate” to describe the “natural” samples. This relative terminology is indefinite and, as a result, any terms defined by this indefinite language is indefinite. For example, “very small to very large molecules” in line 6 of the specification is indefinite because the terms “very small” and “very large” are relative terms, which renders the definition of “natural” samples indefinite and/or unclear and, as a result, also renders any claims that use the term “natural” unclear. The terms “very small” and “very large” are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b).

Finally, the Examiner contends that simply listing examples of potential “natural” samples also will not cure the above defect (see Paper No. 9, page 7, paragraph 1 wherein Applicants cite page 8). Here, Applicants have not provided any teachings that would allow a person of skill in the art to extrapolate which compound would be included in this genus from Applicants laundry list of potential “natural” samples.

Accordingly, the 35 U.S.C. 112, second paragraph rejections cited above are hereby maintained.

***Claims Rejections - 35 U.S.C. 102***

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8. Claims 1-14 and 21-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Nash et al (US Patent No. 6,207,861) (Date of Patent is **March 27, 2001**).

For *claim 1*, Nash et al (see entire document) discloses a method for identifying members of a mass-coded combinatorial library which are ligands for a biomolecule wherein said biomolecule can be a protein (see Nash et al, column 2, paragraph 3, “contacting the first biomolecule [e.g., protein] with the mass-coded molecular library, whereby members of the mass-coded molecular library which are ligands for the first biomolecule bind to the first biomolecule to form first biomolecule-ligand complexes and members of the mass-coded library which are not ligands for the first biomolecule remain unbound”; see also column 1, line 58 defining the “biomolecule” as a “protein”), which anticipates claim 1.

For example, Nash discloses mixing a protein target and a natural sample in solution to form a reaction mixture and incubating said mixture under conditions that will allow complex formation (see Nash et al, column 2, lines 30-36), which anticipates claim 1 (1) and (2). Nash discloses passing the reaction mixture through a first size-exclusion column medium that removes from the reaction mixture any small molecular weight compounds (see Nash et al, column 2, lines 36-38; see also column 13, lines 54-67; see also column 15, last paragraph; see also Examples 4-5 and 7-8). Nash discloses subjecting the size-excluded reaction mixture to conditions promoting dissociation of any ligand/target complex into free ligand and free target (see Nash et al, column 2, lines 38-39). Nash discloses subjecting the reaction mixture to a second size exclusion medium



(see Nash et al, column 2, lines 47-40, please note that Applicants “comprising” language does not preclude the addition of a second library).

*Response*

9. Applicants’ arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants’ newly amended and/or added claims and/or arguments.

Applicants argue [1] that the “synthetic” combinatorial library disclosed in Nash et al is distinguishable from the “natural” samples disclosed in the presently claimed invention (see Paper No. 8, paragraph bridging pages 8-9), [2] Nash et al applies a single filtering step that removes unbound small molecules, such as, using a gel filtration. Therefore Nash et al. was intent only on separating out unbound, small ligands from larger complexes of small ligands bound to target, which were then subjected to mass spectrometry (see Paper No. 9, page 9, paragraph 1), [3] Nash does not provide the specific starting material nor the conditions required for practicing the method of the invention. Specifically, Applicants argue that their method is “simpler” and does not require the same method steps and reagents (see Paper No. 9, page 9, last paragraph), [4] Nash et al also does not teach nor anticipate, removing “larger molecular weight compounds”, including the target when it is large, prior to mass spectrometry (see Paper No. 9, page 10, paragraph 1), [5] The cited art fails to teach or even suggest the need to apply another size-exclusion step (Applicants’ step (5), e.g., ultrafiltration), to remove large molecules also

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present in the natural sample and the target (see Paper No. 9, page 10, paragraph 1), [6] Even less does the prior art teach or suggest combining two size-exclusion steps as in Applicants' claimed screening method i.e., removing "small" molecular weight compounds first (Applicant's step (3)) and then removing larger molecules prior to mass spectrometry (Applicants' step (5)) (see Paper No. 9, page 10, paragraph 1), [7] The cited art also fails to anticipate the particular dimension of the size-exclusion media used by Applicants (e.g., size exclusion gel filtration or HPLC column and ultrafiltration membrane), as recited in the dependent claims. For instant, Applicants' second size-exclusion medium excludes molecules having a molecular weight of at least 3000 Daltons or more (claim 11), preferable 10,000 Daltons or more (claim 10) (see Paper No. 9, page 10, paragraph 1), [8] Applicants method enables "high throughput" screening (see Paper No. 9, page 10, second paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that as stated above under the 35 U.S.C. § 112, second paragraph rejection (which is incorporated in its entirety herein by reference) it is not clear what a "natural" sample is and, as a result, Applicants arguments are moot.

[2] As an initial matter the Examiner notes that it is not clear what Applicants are arguing here. Applicants merely provide a statement trying to characterize the Nash et al reference (i.e., Nash et al was intent only on separating out unbound, small ligands from larger complexes of small ligands bound to target"), but they do not state how the claims differ from this characterization. Therefore, Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without

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specifically pointing out how the language of the claims patentably distinguishes them from the references.

[3] The Examiner contends that Nash et al does anticipate the present invention as outlined by the original and newly modified rejection above. Furthermore, the Examiner contends that it does not matter if Applicants' actual method is "simpler" because Applicants' claimed method uses "comprising" terminology i.e., it can include additional steps.

[4-5] The Examiner contends that the Nash et al reference discloses the removal of molecules "larger than a second preset value" because the "preset value" could be zero and Nash et al discloses the removal of molecules that are larger than zero daltons.

[6] The Examiner contends that Nash et al does teach the use of "two" size-exclusion steps wherein molecules that are "smaller" and/or "larger" than a preset value are removed because the "preset" value could be set to anything and, as a result, the limitation reads on all sizes.

[7] The Examiner contends that limitations stated in claims 10 and 11 would be immediately envisioned by one of ordinary skill in the art.

[8] As an initial matter the Examiner notes that it is not clear what Applicants are arguing here. Applicants merely provide a statement that their method is useful for high throughput screening, but they do not state that the claimed method retains these limitation nor do they state that the prior art does not contain these limitations. Therefore, Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

***Claim Rejections - 35 USC § 103***

10. Claims 1-14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaur et al (Kaur, S.; McGuire, L.; Tang, D.; Dollinger, G.; Huebner, V. "Affinity Selection and Mass Spectrometry-Based Strategies to Identify Lead Compounds in Combinatorial Libraries" *Journal of Protein Chemistry* **1997**, *16*, 5, 505-511) (see IDS) and Van Breemen et al (Van Breemen, R. B.; Huang, C. -R.; Nikolic, D.; Woodbury, C. P.; Zhao, Y. -Z.; Venton, D. L. "Pulsed Ultrafiltration Mass Spectrometry: A New Method for Screening Combinatorial Libraries" *Anal. Chem.* **1997**, *69*, 2159-2164).

For *claim 1*, Kaur et al (see entire document) teaches a method for identifying lead compounds in a combinatorial library wherein a target protein is mixed with a combinatorial library of potential ligands under conditions that allow for complex formation using hyphenated SEC-LC(reverse phase)-ESI technology (see Kaur et al, section 2.2; see also figure 1; see also first paragraph under Results and Discussion section). First, Kaur et al discloses passing the reaction mixture through a first size-exclusion column to remove small molecular weight compounds that are less than a first preset value (see Kaur et al, paragraph bridging pages 506-507). Second, Kaur et al discloses subjecting the size-excluded reaction mixture to conditions promoting

dissociation of any ligand/target complex into free ligand and free target via a reverse-phase LC column (see Kaur et al, page 507, column 1, paragraph 1).

For *claims 2-3*, Kaur et al shows the separation of molecules that are in the range of 350-800 daltons (see Kaur et al, page 507, column 2, paragraph 1; see also figures 2a-c).

For *claim 4*, Kaur et al discloses a Pharmacia HR 10/10 size exclusion HPLC column (see Kaur et al, page 506, section 2.2).

For *claim 5*, Kaur et al discloses the use of 50/50/1 to 30/70/1 water/acetonitrile/acetic acid (see Kaur et al, page 506, column 2, paragraph 1).

For *claims 13-14*, Kaur et al discloses referencing the masses of the ligands identified with those predicted in the compound library (see Kaur et al, page 507, column 1, paragraph 1).

For *claims 21-22*, Kaur et al discloses the use of CID-MS/MS to confirm the identity and structure of any potential ligands (see Kaur et al, page 507, column 1, paragraph 1).

The prior art teachings of Kaur et al differ from the claimed invention as follows:

For *claims 1, 5-12*, Kaur et al is deficient in that it does not teach the use of a second size exclusion medium. Kaur et al only teaches the use of a reverse-phase LC cartridge coupled to an electrospray mass spectrometer i.e., an LC-MS (note MS represents applicants elected method of detection i.e., mass spectrometry) step to dissociate the ligand/target complex instead of the required SEC-MS (see Kaur et al, page 507, column 1, paragraph 1).

However, Van Breemen et al teaches the following limitations that are deficient in Kaur et al:

For *claim 1 and 5-12*, Van Breemen et al (see entire document) teaches the use of a hyphenated ultrafiltration-mass spectrometry technique i.e., ultrafiltration-MS that can be used as a substitute for LC-MS (see Van Breemen et al, page 2160, column 1, last paragraph, “[a] liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the HPLC column”). Furthermore, Van Breemen et al discloses the use of organic solvents and acids to disrupt the protein-ligand complex (see Van Breemen et al, Experimental section; see also page 2163, column 2, paragraph 1). Van Breemen et al also discloses the use of an ultrafiltration YM-10 (from Amicon) membrane and states that the cutoff of the membrane should be selected so as to retain the target protein i.e., if the protein is 40,000 than the cutoff must be less than 40,000 (e.g., a 10,000 molecular weight cutoff was used for the 41,250 MW adenosine deaminase target protein).

It would have been obvious to one skilled in the art at the time the invention was made to substitute the “ultrafiltration-MS” as taught by Van Breemen et al for the “LC-MS” portion of the hyphenated SEC-LC-MS method as taught by Kaur et al (i.e., a hyphenated SEC-ultrafiltration-MS method would result after substitution) because Van Breemen et al explicitly states that the ultrafiltration-MS can be substituted for LC-MS and the method of Kaur et al (see Van Breemen, page 2161, column 1, paragraph 3, “A liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the HPLC

column [i.e., ultrafiltration-MS was substituted for LC-MS]). Furthermore, the two references (i.e., Van Breemen et al and Kaur et al) represent overlapping subject matter i.e., both are drawn to methods for identifying ligands to target proteins in natural samples using solution phase size exclusion techniques (see abstracts and introductory sections to both papers). Furthermore, one of ordinary skill in the art would have been motivated to substitute the ultrafiltration method as taught by Van Breemen et al for the reverse-phase LC method as taught by Kaur et al because Van Breemen teaches that unlike the method of Kaur et al the target protein could be reused in the Van Breemen method which would enable a considerable cost savings for precious target protein samples (see Van Breemen et al, page 2164, last paragraph, "Unlike these other mass spectrometry-base screening methods, pulsed ultrafiltration mass spectrometry allows the solution-phase receptor to be recovered or reused, which is a distinct advantage when the receptor protein is expensive or in short supply. In addition, only pulsed ultrafiltration mass spectrometry allows library compounds to be extracted from a dilute solution and concentrated onto the receptor molecule, which overcomes common library solubility limitations"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Van Breemen et al teaches a specific example wherein the ultrafiltration was successfully used to replace LC (see Van Breemen et al, entire document, especially page 2160, column 1 paragraph 3; see also Results and Discussion Section).

*Response*

11. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue [1] that their invention uses "natural" samples whereas Kaur et al uses combinatorial synthetic methods to make the samples (see Paper No. 9, page 11; see also page 12, the beginning of paragraph 2), [2] Kaur et al is distinguishable from the present invention such that its teaching or suggestion cannot make the present invention obvious (see Paper No. 9, page 12, paragraph 1), [3] Kaur et al fails to teach the second size exclusion column (see Paper No. 9, page 12, paragraph 2), [4] Van Breemen et al. fails to cure the deficiencies found in Kaur et al. Van Breemen et al. also fails to recognize the difficulty of obtaining ligands from complex natural samples, [5] Applicants describe the Van Breemen et al reference and then describe their actual method, [6] the Van Breemen et al. reference fails to teach or suggest providing two different size-exclusion mediums for the efficient isolation of the ligand of interest and [7] the Van Breemen et al., either alone or in combination, fails to teach or suggest the claimed invention.

This is not found persuasive for the following reasons:

[1] The Examiner contends that as stated above under the 35 U.S.C. § 112, second paragraph rejection (which is incorporated in its entirety herein by reference) it is not clear what a "natural" sample is and, as a result, Applicants arguments are moot.



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[2] Applicants' arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants merely make an unsupported statement that Kaur et al is distinguishable. They further describe the Kaur et al reference and also their own specification, but they fail to provide any reason why one is different from the other.

[3] In response to applicant's arguments against the Kaur et al reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[4] The Examiner contends that as stated above under the 35 U.S.C. § 112, second paragraph rejection (which is incorporated in its entirety herein by reference) it is not clear what a "natural" sample is and, as a result, Applicants arguments are moot. Furthermore, the other "deficiencies" are not specified and, as a result, Applicants' arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

[5] Applicants' arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants describe the Van Breemen et al reference and then describe their actual method, but

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fail to make any indication whatsoever as to why the Van Breemen et al reference does not teach the "claimed" method.

[6] In response to applicant's arguments against the Van Breemen et al reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[7] Applicants' arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants have merely made an unsubstantiated statement.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

### *Conclusion*

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of

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a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon D. Epperson, Ph.D.  
August 25, 2003

BENNETT CELSA  
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Bennett Celsa', written in a cursive style.